Remarks

Upon entry of the foregoing amendment, claims 71, 72, 74-87 and 89-97 are pending in this application. Claims 73 and 88 are newly canceled herein without prejudice or disclaimer. Claims 1-70 were previously canceled without prejudice or disclaimer. Claims 71, 72, 74, 81, 84-87, 89 and 94 have been amended. Claims 96 and 97 are newly added herein. Applicants reserve the right to pursue the subject matter of the cancelled claims in a continuing or divisional application. Claims 71 and 81 are the independent claims.

Support for the amendments to claim 71 are found, for example, in original claim 1 for the concept of a formulation comprised of at least one molecule which is an antigen and where the formulation does not include heterologous adjuvant; in original claim 2 ("wherein the molecule also has adjuvant activity"); page 3, lines 7-9, for the concept of a single molecule having both antigenic and adjuvant properties ("we have shown cholera toxin to be immunogenic acting as both antigen and adjuvant"); page 19, lines 24-25 ("Adjuvants which are themselves antigenic would also be useful as antigen in the present invention."); page 31, lines 11-13, for the concept of a single molecule of the formulation containing both adjuvant and antigen activities; Example 1, pages 56-57, showing an antigenic response to CT alone (see, *e.g.*, Table 1); and, elsewhere throughout the specification.

Claims 71 and 81 have been amended to change the phrase "transcutaneous immunization" to "inducing an antigen-specific immune response" in order to track the already existing language in part (c) of the claim.

Claims 72 and 87 have been amended to remove the phrases "tetanus toxin" and "diphtheria toxin."

Claim 74 has been amended to change the claim dependency in view of the cancellation of claim

73 and to more clearly claim the invention.

Claims 84, 86, 89 and 94 have been amended to correct grammatical errors (84, 86, 89) to more clearly claim the invention (89) and to correct claim dependency from a newly canceled claim (89).

Claim 85 has been amended to delete the word "heat." Support for amended claim 85 is found, for example, in Example 44 (page 125), Table 43, page 126, showing an antibody response to killed rabies virus.

Support for new claims 96 and 97 is found, for example, on page 12, lines 9-11 ("A 'patch' refers to a preferred embodiment which includes a solid substrate (e.g., medical dressing) as well as at least one active component."); page 16, lines 14-26 ("The patch may include additional antigens ... ." and, ".. a single molecule of the formulation may contain both adjuvant and antigen activities (specification, page 31, lines 11-13)); and, elsewhere throughout the specification.

No new matter is believed to have been added by this amendment. In view of the amendments and following remarks, reconsideration of the rejections and withdrawal thereof is respectfully requested. The Office Action dated March 22, 2004 has been carefully reviewed and the foregoing amendments and arguments are made in response thereto.

Rejection of claims 71, 72, 75-87 and 90-95 under 35 U.S.C. § 112, first paragraph

The Office rejected claims 71, 72, 75-87 and 90-95 under 35 U.S.C. § 112, first paragraph, because the specification while being enabled for "a method for transcutaneous immunization comprising applying a formulation to hydrated skin," (emphasis in the original) does not reasonably provide enablement for:

A) a method for TCI comprising applying diptheria toxin (DT) (i.e., claims 72 and 87);

B) a method for TCI wherein the induced immune response recognizes a lipopolysaccharide;

C) a method for TCI wherein the antigen specific immune response recognizes an antigen selected from the group consisting of influenza virus hemagglutinin (HA), influenza virus nucleoprotein (NP), *Hemophilus influenza* B polysaccharide conjugate (Hib-PS), and *Escherichia coli* colonization factor CS6 (i.e., claim 86). The Office maintained the rejections for reasons of record first set forth in the paper mailed 12/04/01 and in the papers mailed 08/06/02 and 06/03/03. The rejection is respectfully traversed.

The term "hydrated" is not a critical limitation and is <u>not</u> required for patentability

At the outset, Applicants note that Office implicitly suggests the claim is enabled for a method comprising, *inter alia*, application to "hydrated" skin.[1] No rejection has explicitly been made to date broadly alleging the claims lack enablement unless and until amended to include the term "hydrated."[2] Applicants assert that application of the formulation to "hydrated" skin is merely a variation of the method of the invention and is **not** a critical limitation. The specification provides more than sufficient support for a method of inducing an immune response where the skin is **not** hydrated. See, for example, the following citations showing both literal and experimental support in the specification for application of a formulation to **non-hydrated** skin:

1. page 35, lines 22-24: "Optionally, hydration or occlusive dressings may be used in the transcutaneous delivery system in addition to activation of the adjuvant." (explaining hydration is not a critical limitation);

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1 See, Final Office Action, dated Aug. 6, 2002, where the Office first makes the statement in a rejection under 35 USC 112, first paragraph, that "..because the specification, while being enabled for a method of TCI comprising applying a formulation...to hydrated skin, does not reasonably provide enablement for... ." The Office repeated the statement in the rejection in the Office Action dated June 3, 2003 and in the Final Office Action dated March 22, 2004. However, the Office has not explicitly rejected the claims for failure to claim "hydrated" skin and Applicants believe such a rejection would be unwarranted, as explained above.

2 A rejection under 35 USC 112 (2) over the word "hydrated" in original claim 10 was made in the Office Action dated Dec. 4, 2001. In the Reply dated June 4, 2002, Applicants amended claim 10 to make it clear that it was the skin being hydrated.

2. page 40, lines 6-21: "The transcutaneous immunization system may be applied directly on the skin and allowed to air dry..."; "The formulation may be applied directly to the skin" (explaining hydration is not a critical limitation);

3. page 59, Example 4: LT mixed in saline and placed directly on mouse skin (showing an immune response obtained to a formulation placed on **non-hydrated** mouse skin and that hydration is not a critical limitation);

4. page 71, Example 17: CT and CTB mixed in saline placed directly on mouse ears (showing an immune response obtained to a formulation placed on **non-hydrated** mouse skin and that hydration is not a critical limitation);

5. page 83, Example 24: CT mixed in saline was placed directly on mouse ear (showing an immune response obtained to a formulation placed on **non-hydrated** mouse skin and that hydration is not a critical limitation);

6. page 94, Example 29: OVA and CT in PBS placed directly on back skin of mice (showing an immune response obtained to a formulation placed on **non-hydrated** mouse skin and that hydration is not a critical limitation);

7. page 99, Example 32: CT in saline placed directly on bare skin (showing an immune response obtained to a formulation placed on **non-hydrated** mouse skin and that hydration is not a critical limitation);

8. page 106, Example 34: CpG and DT in PBS placed directly on back (showing an immune response obtained to a formulation placed on **non-hydrated** mouse skin and that hydration is not a critical limitation);

9. page 149, Example 60: CT in saline or dry powder placed directly on skin (showing an immune response (see table 59) obtained to a formulation placed on **non-hydrated** mouse skin and that hydration is not a critical limitation);

10. page 151, Example 61: CT in dry powder form or CT in saline placed directly on skin (showing an immune response obtained to a formulation placed on **non-hydrated** mouse skin and that hydration is not a critical limitation); and,

11. page 153, Example 62: CT in wet patch; CT in dry patch; CT in dry powder form (showing an immune response obtained to a formulation placed on **non-hydrated** mouse skin and that hydration is not a critical limitation).

Thus, there are at least eleven specific examples from the specification showing that hydration is **not** a critical limitation to the invention as claimed. Importantly, the specification provides experimental results showing that dry formulations applied to dry skin will provide an immune response. In view of the more than sufficient support in the specification showing that hydration is not a critical limitation, claims 71 and 81 as now amended do not include the term "hydrated."

Regarding A) above (see page 7), the term "diphtheria toxin" has been deleted from newly amended claims 72 and 87 without prejudice or disclaimer, thus mooting the rejection.

Regarding B) above (see page 7), no current claim claims lipopolysaccharide. Therefore, the rejection is moot.

Regarding C) above (see page 7), support for the claimed subject matter

> "antigen specific immune response recognizes an antigen selected from the group consisting of influenza virus hemagglutinin (HA), influenza virus nucleoprotein (NP), *Hemophilus influenza* B polysaccharide conjugate (Hib-PS), and

Escherichia coli colonization factor CS6"

is found, for example, in Table 42, page 124 (showing HA results); in Table 21, page 85 (showing Hib-PS results); in Table 31, page 105 (showing CS6 results); on page 146, Table 56 showing (influenza nucleoprotein (NP)) results. Following is an expanded review of each of these supports:

1. Influenza virus hemagglutinin (HA)

Example 43, page 123, details the experimental protocol used to demonstrate an antigen specific immune response was induced to HA using the method of claim 81. Specifically, in Example 43, the animals were immunized with 100 micrograms cholera toxin (CT) and 100 micrograms influenza hemagglutinin (HA) at one site or two sites on the back. HA and CT were applied at 0, 3 and 5 weeks. Seven weeks after the primary immunization the animals were bled and the anti-HA titers determined using "ELISA IgG (H + L)" as described elsewhere in the specification. The specification states the results of the experiment are shown in Table 42. Table 42 presents results showing the amount (ELISA units) of anti-HA IgG produced 7 weeks after immunization, thus clearly demonstrating production of an antigen specific immune response to HA.

2. Influenza virus nucleoprotein (NP)

Example 56, page 145, (influenza nucleoprotein (NP)) details the experimental protocol used to demonstrate an induction of an antigen specific immune response to NP using the methods of the invention. Specifically, in Example 56, groups of mice received one of the following treatments:

a) 100 micrograms of a DNA plasmid (pCMV-NP) encoding for influenza nucleoprotein in 100 microliters of saline was applied to hydrated skin on the backs of mice;

b) 100 micrograms of the DNA solution described in a) above was applied to hydrated skin on the backs of mice except that the skin was tape-stripped three times; and,

c) 100 micrograms of the DNA solution described in a)above was applied to hydrated skin on the backs of mice except that the skin was tape-stripped three times and the DNA solution included 100 micrograms of LT.

Sixteen days after the primary immunization the animals were bled and the anti-NP titers determined using an ELISA assay. The results are shown in Table 56 and clearly demonstrate all three immunization groups developed anti-influenza NP titers as compared with titers in serum collected from the same animals prior to immunization.

3. Hib-PS results

Example 25, page 85, discloses the experimental protocol employed to demonstrate an antigen specific immune response was raised to *H. influenza* b polysaccharide conjugate (Hib-PS) using the methods of the invention. Briefly, mice were treated with Hib-PS alone or Hib-PS and CT and the antibodies were determined using ELISA on serum collected three weeks after the second immunization. While Hib-PS alone induced a small but detectable antibody response, the addition of CT stimulated a far stronger immune response to Hib-PS. The results are shown in Table 21 and clearly demonstrate an immune response to Hib-PS.

4. *Escherichia coli* colonization factor CS6

Table 31, page 105, demonstrates the induction of immunity again CS6 colonization factor following transcutaneous immunization with cholera toxin (CT). Briefly, as discussed in Example 33, mice were treated with CS6 alone or a combination of CS6 and CT and immunization was repeated 4 and 8 weeks later. Twelve weeks after the primary immunization the animals were bled and anti-CS6 titers determined. The results are shown in Table 31. Specification page 104, lines 21-23, discusses the nature of the antigen specific result obtained, noting that "The titers to CS6 are among the highest antibody titers seen to date for immunization by transcutaneous delivery and suggests that LPS, an additional adjuvant, may augment the immune response induced by CT."

Thus, contrary to the allegations of the Office, the specification provides abundant enablement for the invention as claimed. If the Office maintains this rejection, the Office is respectfully requested to provide a detailed explanation giving the reasons why the results presented in Table

42 (obtained by the method set forth in Example 43), in Table 56 (obtained by the methods of Example 56) and Table 31 (obtained by the method set forth in Example 33) are not considered to enable one of ordinary skill in the art to practice the invention as claimed. The rejection is believed to not be applicable to new claims 96 and 97 since claims 96 and 97 depend from claims 71 and 81, respectively, allowable in view of the amendments and arguments above. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph (written description)

The Office rejected claims 71-95 under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention in that the disclosure does not reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. The rejection is respectfully traversed.

The Office alleges the specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) "a modified ADP ribosylating exotoxin ....modified to be less toxic" (Claims 71 and 81);

B) the" ADP-ribosylating exotoxin.....tetanus toxin" (claims 72 and 87);

C) a "formulation comprised of antigen and adjuvant" (claim 81); and,

D) "heat killed rabies virus" (claim 85).

Regarding part A), the Office alleges lack of support for the broad phrase "modified to be less toxic." However, contrary to the position of the Office, literal support for the wording and support for the concept is found throughout the specification. For example, original claim 53 recites the language "....(ADP-ribosylating exotoxin).....**modified to be less toxic to the organism than non-modified** ADP-ribosylating exotoxin." (emphasis added). Support for the claim language, is also found, for example, on page 34, lines 21-24, describing modified ADP-ribosyl transferases. A modified ADP-ribosyl transferase is obtained by inactivating the catalytic

activity of the ADP-ribosyl transferase. See, page 34, lines 22-24, stating "The toxins retain the binding capabilities, but lack the toxicity, of the natural toxins." Support for the concept of modified ADP-ribosylating exotoxins, wherein the modification results in the exotoxin lacking the toxicity of the natural toxins, is found in the specification as filed. Thus, contrary to the position of the Office, the specification provides support for the broader "modified to be less toxic" phrase.

Regarding part B), claims 72 and 87 have been amended to delete the phrase "tetanus toxin" without prejudice or disclaimer.

Regarding part C), the Office alleges the phrase "formulation of comprised of antigen and adjuvant," lacks written description and does not find support in claim 1, noting that "claim 1 specifically excluded a formulation comprising a separate antigen and adjuvant. However, claim 1 was not cited for support for the phrase "antigen and adjuvant." Contrary to the Office's arguments, claim 81 finds support in original claim 1 in the preamble of original claim 1 ("A method for transcutaneous immunization") and in part (c) of claim 1 ("....an antigen specific immune response in said organism, wherein at least one epitope of said antigen is recognized"). Support for claim 81 for the concept of a formulation "comprising a separate antigen and adjuvant" is found at least in Examples 19-22, 25, 29-31 and elsewhere throughout the specification.

The Office asserts that the examples disclosing specific formulations administered to specific mouse strains cannot be considered sufficient written description to support generic methods. The Office alleges that the examples disclosing the administration of specific formulations such as CT and BSA to BALB/c mice cannot support claims drawn to generic administration of any formulation to any subject. However, contrary to the Office allegations, the specification provides more than a single example of co-administration of antigens and adjuvant. For instance, Table 13 discloses results obtained using diphtheria toxoid (DT) and pertussis toxin

(PT) and that the PT acted as an adjuvant for the DT antigen; Example 19 discloses use of sequestrin with CT and that CT acted as an adjuvant for the sequestrin antigen; Example 21 discloses use of FLUSHIELD subvirion influenza vaccine (a mixture of virally derived antigens) with CT and that CT acted as an adjuvant for the FLUSHIELD antigens; Example 22 discloses use of ETA or LT with DT and that both ETA and LT acted as adjuvants for DT; and Example 25 discloses Hib-PS and CT and that CT acted as an adjuvant for Hib-PS antigens. Thus, the specification discloses that a wide and comprehensive variety of different antigens and different adjuvants will work when used according to the methods of the invention.

As the Office is aware, the possible presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling). Applicants assert the specification clearly provides methods (See, for example, Examples 19-22, 25, 29-31) to determine which embodiments within claims 71-95 are operable and which are not. (A disclosure of a large number of operable embodiments and the identification of a single inoperative embodiment did not render a claim broader than the enabled scope because undue experimentation was not involved in determining those embodiments that were operable. *In re Angstadt*, 537 F.2d 498, 502-503, 190 USPQ 214, 218 (CCPA 1976)).

Contrary to Office arguments, the specification provides support for the full scope of the claims and adequate written description for the claimed invention. If the Office maintains this rejection, the Office is respectfully requested to provide a detailed explanation of the reasons why the cited support above fails to overcome the rejection.

Regarding part D), claim 85 has been amended to delete the term "heat" and the rejection is now believed to be moot. The Office also asserts "a specific example cannot support a generic claim." However, claim 85 does not claim a genus.

As the Office knows, the written description requirements of 35 U.S.C. § 112, first paragraph, are distinct from the enablement requirements of 35 U.S.C. § 112, first paragraph. While the claims are said to be rejected for "lack of written description" statements to the effect that "a specific example cannot support a generic claim" and "lack of support for the broad phrase 'modified to be less toxic'" would seem to indicate the Office has rejected the claims for allegedly lacking enablement, not written description. In any case, both grounds of rejection have been addressed, above. The rejection is believed to not be applicable to new claims 96 and 97 since claims 96 and 97 depend from claims 71 and 81, respectively, allowable in view of the amendments and arguments above. Reconsideration and withdrawal of the rejection is respectfully requested.

Obviousness-type Double Patenting Rejection over Appl. No. 09/266,803; Appl. No. 10/633,626; Appl. No. 10/701,069 and Appl. No. 10/435,676

The Office provisionally rejected claims 71-95 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-35, 50-77 and 79-111 of copending Application No. 09/266,803; over claims 2, 5, 6, 11, 19 and 32 of copending Application No. 10/633,626; over claims 2, 5, 6, 11, 19 and 32 of copending Application No. 10/701,069 and claims 1, 5, 12, 14 and 17 of copending Application No. 10/435,676.

Regarding Appl. No. 09/266,803 ('803), Applicants will submit a terminal disclaimer over the '803 application upon indication by the Office of allowable subject matter in the instant application. In view of the amendments to the claims and cancellation of other claims, it is believed the provisional rejections are the only rejections remaining in this application. As the Office is aware, once the "provisional" double patenting rejection in one application is the only

rejection remaining in that application, the rejection should be withdrawn and the application permitted to issue as a patent (MPEP § 804 (I)(B), page 800-19, February 2003).

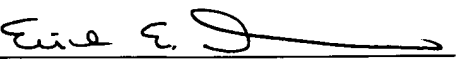
Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicants respectfully request reconsideration and the timely allowance of the pending claims. A favorable action is awaited. Should the Examiner find that an interview would be helpful to further prosecution of this application, the Examiner is invited to telephone the undersigned at his convenience.

Except for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. § 1.16 and § 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310.

This paragraph is intended to be a **Constructive Petition for Extension of Time** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully submitted,
Morgan, Lewis & Bockius LLP



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